Institut für Pharmazeutische Technologie der Heinrich-Heine-Universität Düsseldorf, Germany

Control and stability of drug release from diffusion pellets coated with the aqueous quaternary polymethacrylate dispersion Eudragit® RS 30 D

B. C. Lippold and R. Monells Pagés

The addition within compatibility limits of the pore formers hydroxypropyl methylcellulose (HPMC) and hydroxy ethylcellulose (HEC) to coatings of the quaternary polymethacrylate dispersion Eudragit® RS 30 D enables drug release to be controlled without problems. 20 and 15%, respectively, of these pore formers are suitable for release within 8 h of theophylline from pellets with a coating thickness of about 30 µm. A 10% addition of plasticizer, water soluble triethyl citrate (TEC) or water insoluble dibutyl phthalate (DBP), lowers the minimum film forming temperature (MFT) from 48 to 17 and 26 °C, respectively. The MFT is scarcely influenced by the pore formers. However, the plasticizers may modify the effect of the pore formers: HPMC is more effective in the presence of DBP. In spite of the preparation of the coatings at a bed temperature about 20 °C above MFT, the release from the diffusion pellets is not stable during storage. Only curing in an oven or in the fluidized bed up to a certain limiting release rate at 80 °C for 1 h results in stable products. Increased relative humidity allows reduction of the curing temperature. The water soluble additives polyoxy ethylene (PEG) and polyvinyl pyrrolidone (PVP) and insoluble additives are ineffective as pore formers.

1. Introduction

Polymer coatings for controlled drug release generally require the addition of plasticizers and pore formers. Plasticizers not only improve the mechanical properties of the polymer film [1, 2], but also decrease the minimum film forming temperature (MFT) so that only moderate bed temperatures are necessary [3]. Furthermore, they increase the permeability of the coatings [4–7]. However, they may also cause stickiness of the coatings [8]. When adding lipophilic, sparingly water soluble plasticizers to polymer dispersions, the long time required for adjustment of the partition equilibrium has to be considered [9–11]. Pore formers increase and control drug release from coated preparations [9, 12–19]. Occasionally, polymer dispersions also contain emulsifiers and preservatives. The resulting complex composition of the coating frequently causes stability problems [20]. Incomplete film formation during coating in spite of exceeding the MFT, that is no or insufficient curing, is the most frequent reason [6, 20–22]. As a consequence, further gradual coalescence by interdiffusion of polymer molecules and thus decrease of release rates may occur during storage [20].

The objective of this study was to develop a polymethacrylate slow release coating based on the aqueous dispersion Eudragit® RS 30 D, whose release rate can be adjusted and is stable during storage.

The water soluble triethyl citrate (TEC) and the practically water insoluble dibutyl phthalate (DBP) are used as plasticizers, each with a concentration of 10%, related to the polymer. Water soluble polymers, namely hydroxypropyl methylcellulose (HPMC), hydroxy ethylcellulose (HEC), polyoxy ethylene (PEG) and polyvinyl pyrrolidone (PVP) are added as pore formers (10% related to the coating). Insoluble additives are also studied as pore formers: microcrystalline cellulose (Avicel), highly porous amorphous silica (Syloid) and titanium dioxide (TiO_2), at 20% related to the coating. Theophylline pellets with a diameter of 1.0 to 1.4 mm are coated in a fluidized bed under controlled conditions up to a coating level of 15% and a resulting film thickness of about 30 µm. The coated pellets are cured in an oven at different temperatures until a limiting release rate is obtained ("limiting curing condition", "sufficient curing"). These limiting curing conditions have to be determined separately for every preparation. Scanning electron microscopy demonstrates smooth surfaces and homogeneous cross sections of the coatings of sufficiently cured pellets [21]. Curing TEC and HEC containing coated pellets in the fluidized bed is completely equivalent to curing in the oven. The reproducibility of the process is optimal [21].

2. Investigations, results and discussion

2.1. Properties of the polymer dispersions and prepared films

Table 1 shows the MFTs of Eudragit® RS 30 D with 10% plasticizer (TEC or DBP) with and without the different pore formers after sufficient stirring and standing time [11]. The MFTs with and without pore formers do not differ significantly, except for certain combinations of Syloid and also for TiO_2. Only dispersions without plasticizer show a decrease of MFT with increasing concentration of the pore formers HPMC and HEC from 48 to 44 and 40 °C, respectively, at a concentration of 20% [21].

The glass transition temperatures Tg of poured films are measured by differential scanning calorimetry (DSC) and determined at the 50% transformation point (Tg-midpoint). The thermograms show no clear differences between the first and second heating (Fig. 1). Thus, no conclusions concerning the effect of curing of these films can be drawn: The Tg values are independent of the drying temperature during film formation. However, Eudragit® RS dry powder exhibits a relaxation peak in the first heating curve (Fig. 2), possibly an effect of storage: Freshly

Table 1: MFT values (°C) of plasticized Eudragit® RS 30 D without and with addition of pore formers

Composition	Pore former (%)							
10% plasticizer	without	HPMC 10	HEC 10	PEG 10	PVP 10	Avicel 20	Syloid 20	TiO_2 20
TEC	17	18	17	18	16	15	22	18
DBP	26	24	20	24	24	22	33	32

($\bar{x}$, range of variation <3 °C, n = 3)

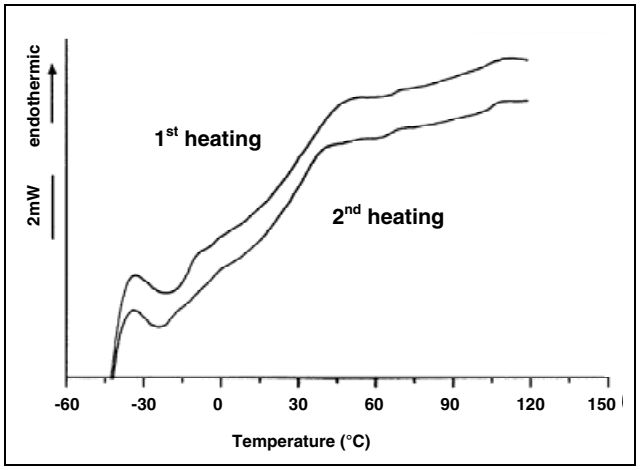

Fig. 1: Typical DSC thermogram of a film of Eudragit® RS 30 D with 10% TEC, 1st and 2nd heating

prepared Eudragit® RS films without additives show no relaxation phenomenon. Table 2 lists the Tg values of the films investigated. As expected, addition of plasticizer reduces the Tg, TEC being more effective as DBP [11]. Of the pore formers only Syloid raises the Tg of the plasticized films comparable to its effect on the MFT and possibly due to adsorption of the plasticizer.

In Fig. 3 the Tg values are plotted versus the MFTs. A fairly good correlation is obtained. The plasticizing effect of water [23–25] partially explains why the MFTs are

Table 2: Tg (°C) of poured films of Eudragit® RS 30 D with added plasticizers and pore formers

Film	n	Tg (°C)
Eudragit® RS (powder)	2	51.0 ± 1.4
Eudragit® RS (film)	2	53.6 ± 3.5
90% RS + 10% TEC	5	29.0 ± 1.6
90% RS + 20% TEC	2	22.0 ± 1.0
90% RS + 10% DBP	9	33.0 ± 1.9
80% RS + 20% DBP	3	21.3 ± 1.5
81% RS + 9% DBP + 10% HEC	2	34.0 ± 1.4
81% RS + 9% DBP + 10% HPMC	2	33.5 ± 0.7
72% RS + 8% DBP + 20% Syloid	3	39.7 ± 2.1
72% RS + 8% DBP + 20% TiO_2	3	34.0 ± 1.0

($\bar{x}$ ± s.d., heating rate 20 °C/min, midpoint)

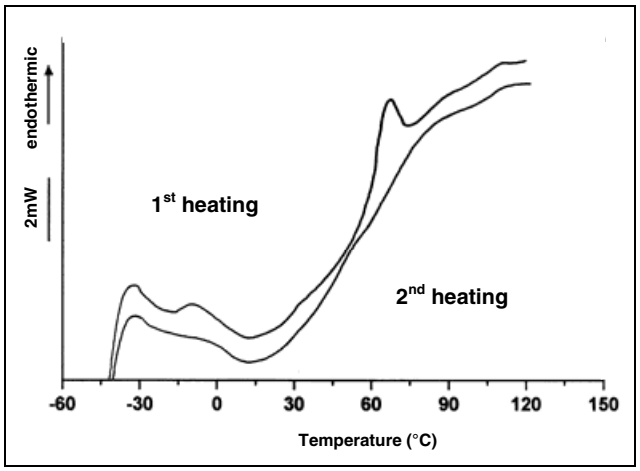

Fig. 2: Typical DSC thermogram of Eudragit® RS powder, 1st and 2nd heating

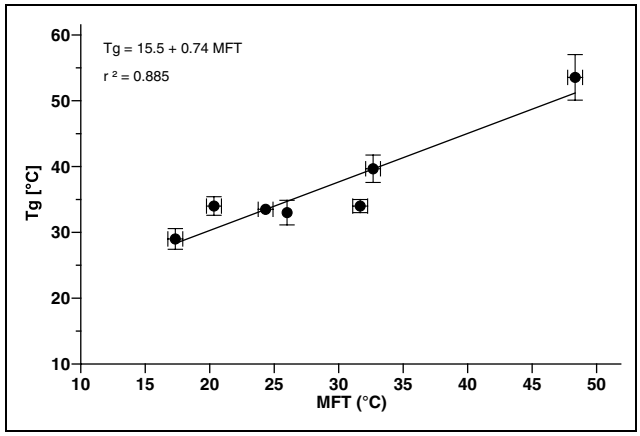

Fig. 3: Correlation between Tg and MFT ($\bar{x}$ ± s.d., n = 2–9)

lower than the Tg values. Capillary attraction and surface tension are also responsible. The ratio MFT/Tg amounts to 0.9, comparable to results with other dispersions [26].

Thermomechanical investigations by the penetration method as shown in Figs. 4–6 give the following conclusions: The pore formers HPMC and HEC are fully compatible with the plastiziced polymer at concentrations of 10 and 15%. The thermograms are the result of homogeneous mixtures of the two polymers in the presence of the plasti-

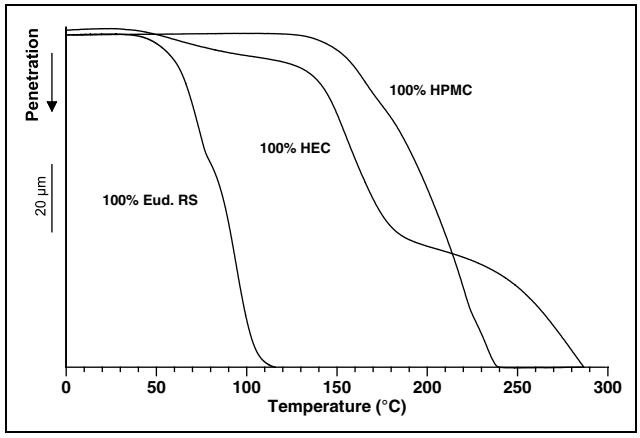

Fig. 4: Typical TMA thermogram of pure films of Eudragit® RS 30 D, HEC and HPMC (heating rate 2 °C/min for Eud. RS, 10 °C/min for HEC and HPMC)

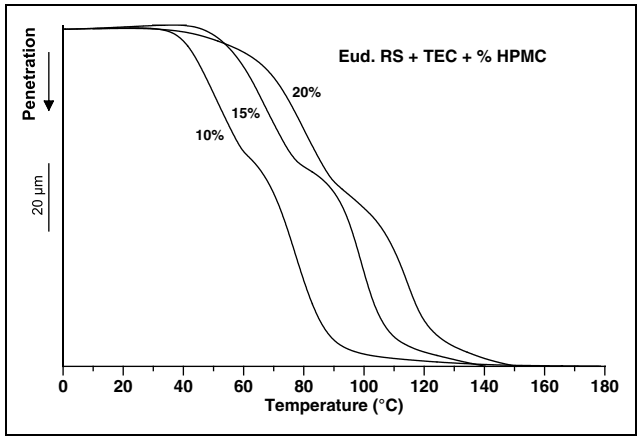

Fig. 5: Typical TMA thermograms of films of Eudragit® RS 30 D with 10% TEC (rel. to Eud. RS) and different amounts of HPMC (rel. to the film)

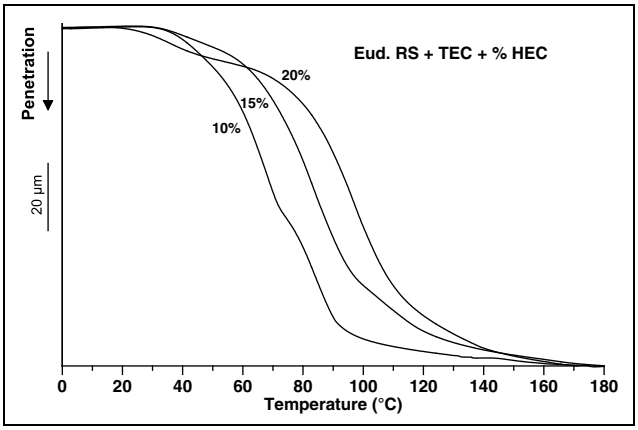

Fig. 6: Typical TMA thermograms of films of Eudragit® RS 30 D with 10% TEC (rel. to Eud. RS) and different amounts of HEC (rel. to the film)

cizers. With 20% of pore former, an additional inflection can sometimes be observed at 104 and 117 °C, respectively, attributed to exceeding the compatibility limit (Figs. 5 and 6). This is more often observed with HPMC. The better compatibility of HEC is confirmed by the fact that plasticizer-free dispersions of Eudragit® RS 30 D only form homogeneous films with HEC. Thermal treatment and storage for 7 months at different humidities do not seem to change the thermograms significantly [21].

2.2. *Effects of the pore formers on the release rate*

Release profiles of sufficiently cured theophylline pellets with different pore formers are shown in Fig. 7. The curing conditions are given in brackets. Curing up to the limiting curing condition results in a considerable decrease in drug release rates, in some cases comparable to the release of diffusion pellets without pore formers [21]. However, there are two exceptions: Coatings with HPMC and even more so with HEC release the drug faster than the other coatings with pore formers. After 24 h, 50% of the drug is released from pellets with HPMC containing coatings. In the presence of HEC, release is complete after 18 h. However, these pellets tend to stick together. In general, these extensively cured coatings behave completely different in comparison with uncured or insufficiently cured diffusion pellets [21]. The reasons for the extremely slow release from coated pellets with the water soluble pore formers PVP or PEG and with the water insoluble additives are incompatibility between the pore formers PVP and PEG and Eudragit® RS and insufficient amounts of the insoluble additives, respectively. If water soluble pore formers are taken up by the coating during film formation, but do not exist in a thermodynamically stable equilibrium state, they try to separate. They diffuse to the surface or accumulate in isolated pools within the film [27], comparable to observations on films from organic or aqueous solutions [28–30]. Thus, these additives are ineffective.

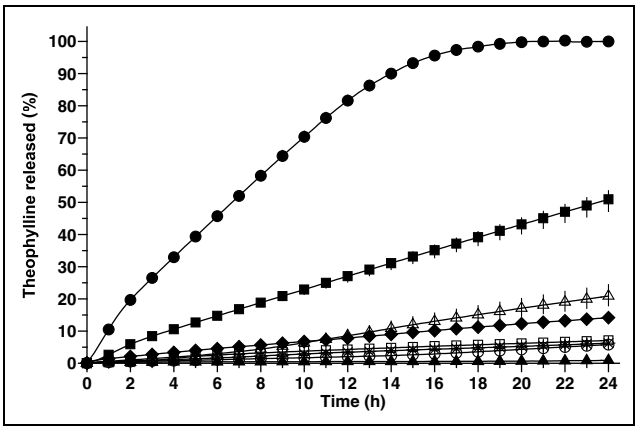

Fig. 7: Influence of different pore formers (PF) on the release of sufficiently cured theophylline diffusion pellets ($\bar{x} \pm$ range of variation, n = 3); coating: Eudragit® RS, 10% TEC (rel. to Eud. RS), 10% water soluble PF or 20% insoluble PF (rel. to the film)
✳ without PF (24 h, 50 °C) ● HEC (1 h, 80 °C)
■ HPMC (24 h, 70 °C) ▲ PEG (1 h, 50 °C)
◆ PVP (24 h, 60 °C) ○ Avicel (1 h, 70 °C)
□ Syloid (1 h, 70 °C) △ TiO_2 (1 h, 70 °C)

2.3. *Effects of plasticizers on the release rate*

The influence of the plasticizers TEC and DBP which differ in solubility on the pore forming capacity of the two effective pore formers HPMC and HEC is shown in Figs. 8 and 9. The release from sufficiently cured pellets with coatings containing HPMC and TEC is about three times faster than from the respective pellets with DBP as plasticizer. Apparently, the pore forming function of HPMC is strongly plasticizer dependent, which means there may be different interactions between HPMC and the plasticized film. HEC behaves differently (Fig. 9). Release is faster with this pore former and is independent of the plasticizer used.

As lipophilic plasticizers like DBP, in contrast to hydrophilic ones, remain in the coating during the release process [15, 21], the Tg of the swollen films (Tg = 33.5–34 °C for dry films, Table 1) is lower than the release temperature of 37 °C.

At 37 °C, the polymer is in a rubbery state and could close pores, arising from migration of pore formers [9, 15]. In contrast, hydrophilic plasticizers like TEC leave the film very quickly [15, 21]. The resulting Tg (51 °C for the dry film, Table 1) is higher than the release temperature. The polymer stays in the glassy state, and pore fusion is not possible [9, 15]. In fact, the effect of pore fusion, a decreasing release rate, is hardly detectable. However, the pore fusion process has been distinctly observed only with rather high concentrations of pore formers [9, 15] (see also 2.4.2.).

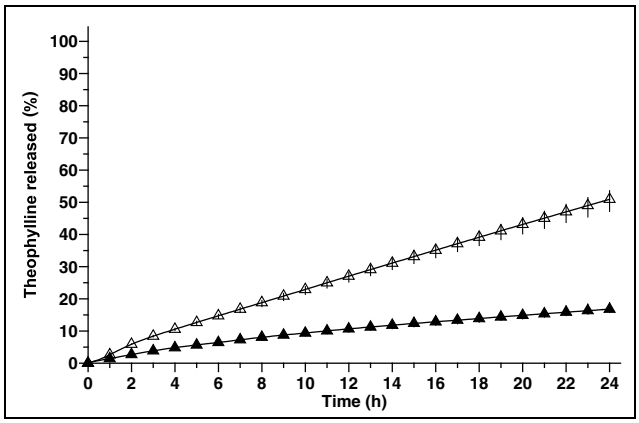

Fig. 8: Influence of plasticizers on the release rate of sufficiently cured theophylline diffusion pellets ($\bar{x} \pm$ range of variation, n = 3); coating: Eudragit® RS, 10% TEC or DBP (rel. to Eud. RS), 10% HPMC
△ TEC (24 h, 70 °C) ▲ DBP (24 h, 70 °C)

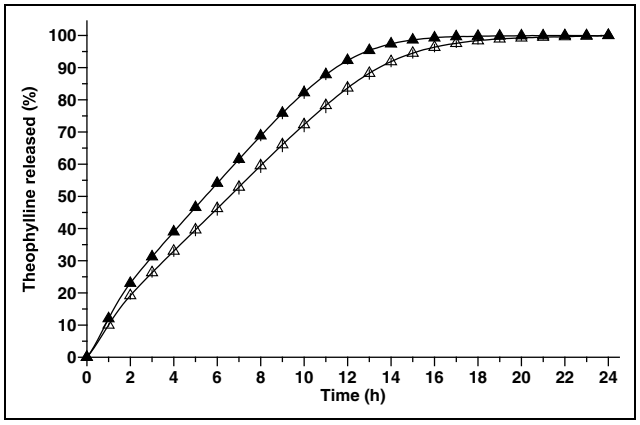

Fig. 9: Influence of plasticizer on the release rate of sufficiently cured theophylline diffusion pellets with HEC ($\bar{x} \pm$ range of variation, n = 3); coating: Eudragit® RS, 10% TEC or DBP (rel. to Eud. RS), 10% HEC (rel. to the film)
△ TEC (1 h, 80 °C) ▲ DBP (1 h, 80 °C)

2.4. HPMC and HEC as pore formers of choice

2.4.1. Influence of pore former concentration on the release

HPMC and HEC are further investigated as the most suitable pore formers. With increasing concentration of the pore formers in the coatings the release rates increase as expected [9, 13, 18, 31, 32]. Fig. 10 shows the influence of different HPMC concentrations (10, 15 and 20% related to the complete film) on the release of sufficiently cured theophylline pellets with TEC as plasticizer in the coating.

As expected, an increase in HPMC concentration increases the release rate. However, this acceleration of release is not proportional to the increase in concentration of the pore former. This also applies for HEC containing coatings (Fig. 11).

Further investigations concentrate on diffusion pellets which release the drug theophylline completely within 8 h. Thus, coatings with 20% HPMC and 15% HEC, respectively, are used.

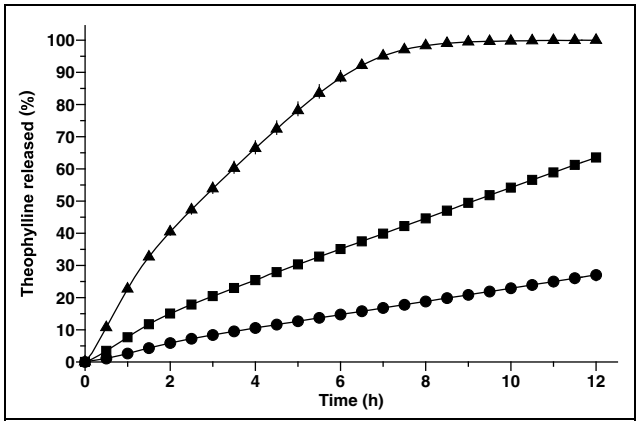

Fig. 10: Influence of HPMC concentration on the release of sufficiently cured diffusion pellets ($\bar{x} \pm$ range of variation, n = 3); coating: Eudragit® RS, 10% TEC (rel. to Eud. RS), curing: 24 h, 70 °C
● 10% ■ 15% ▲ 20%

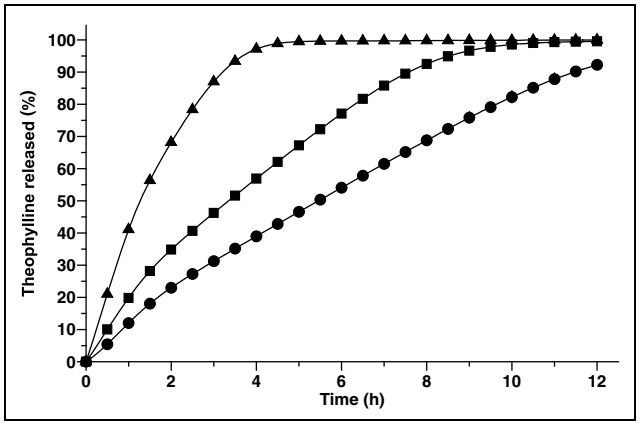

Fig. 11: Influence of HEC concentration on the release of sufficiently cured diffusion pellets ($\bar{x} \pm$ range of variation, n = 3); coating: Eudragit® RS, 10% TEC (rel. to Eud. RS), curing: 1 h, 80 °C
● 10% ■ 15% ▲ 20%

2.4.2. Influence of the release medium, study of single coated pellets

The release rate in 0.1 N-HCl is about 25% slower than in water [21], as already observed by other authors [33–35]. The reason is first of all the reduced swelling of the coating in this medium [35]. Within minutes the uptake of substitution and swelling water amounts to 32 to 40% of the respective films, depending on the presence of plasticizers and pore formers [21].

Deviations from the expected linear course of release when using TEC and DBP as plasticizer (see also 2.3.) are explained in the literature as being a result of a more or less broad distribution of release rates within the pellet population [4, 5, 36–38]. Release rates of single coated pellets are shown in Fig. 12, all of them being slightly curved. Alteration of the coating structure during the release process is possibly the explanation. Small and light diffusion pellets release the drug faster on a percent basis than big and heavy ones, with a deviation from the mean of approximately ±30%. This is due to the higher ratio of area of diffusion to mass and to the thinner coatings of the smaller pellets [39, 40].

2.5. Release stability

Theophylline pellets with a coating of Eudragit® RS 30 D, plasticized with TEC or DBP 10% and with the added pore formers HPMC 20% and HEC 15%, either uncured or cured for 1 h at 80 °C, are stored at room temperature (RT) without conditioning of the relative humidity (r.h.),

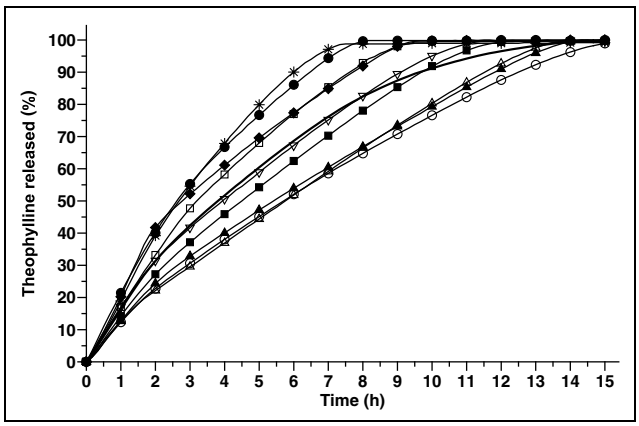

Fig. 12: Release of single theophylline diffusion pellets; coating: Eudragit® RS 76.5% + 8.5% DBP + 15% HEC, curing: 1 h, 80 °C
✳ 1.215 mg ● 1.352 mg □ 1.486 mg
△ 1.807 mg ▽ 1.839 mg ◆ 1.857 mg
■ 2.083 mg ▲ 2.416 mg ○ 2.712 mg – mean

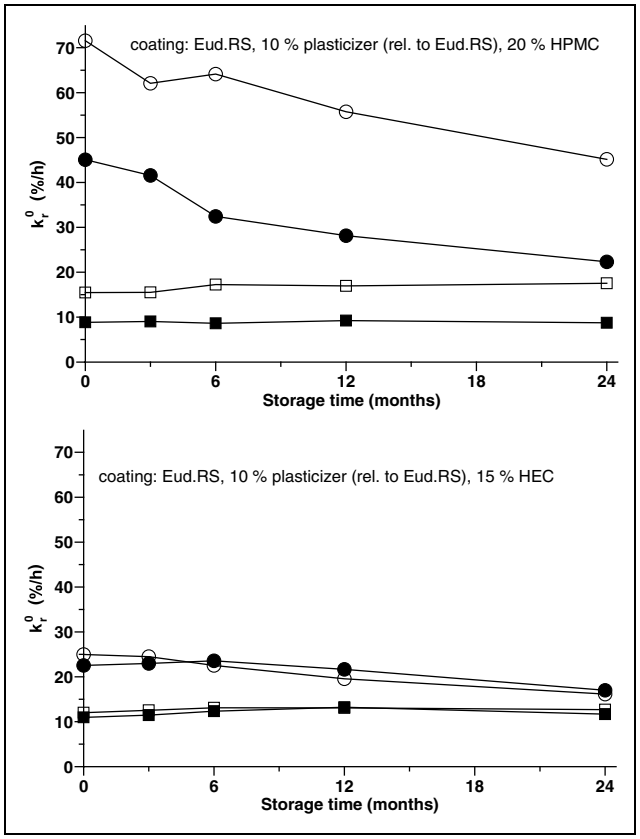

Fig. 13: Influence of storage time on the release rate constant k_r^o of theophylline diffusion pellets at RT
TEC: ○ uncured □ 1 h 80 °C
DBP: ● uncured ■ 1 h 80 °C

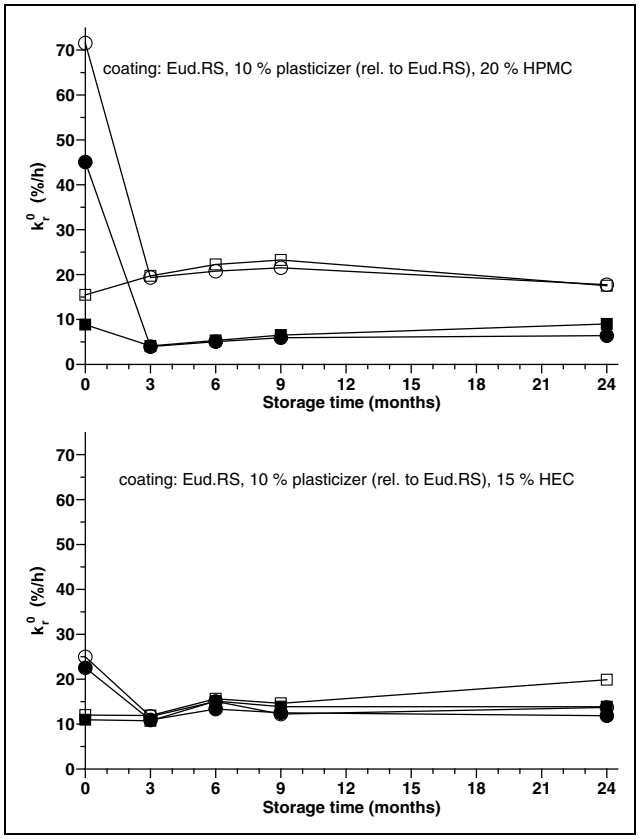

Fig. 15: Influence of storage time on the release rate constant k_r^o of theophylline diffusion pellets at 40 °C and 75% r.h.
TEC: ○ uncured □ 1 h 80 °C
DBP: ● uncured ■ 1 h 80 °C

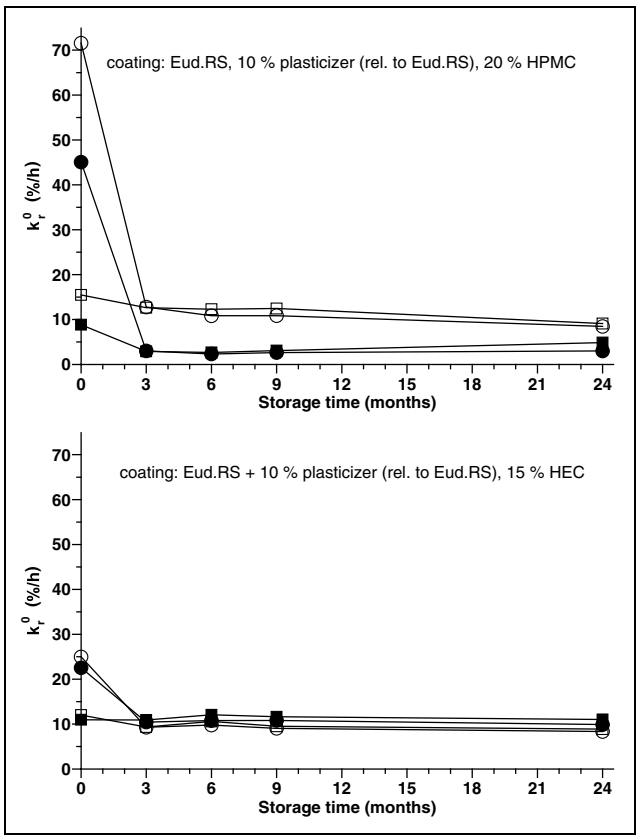

Fig. 14: Influence of storage time on the release rate constant k_r^o of theophylline diffusion pellets at 40 °C and 53% r.h.
TEC: ○ uncured □ 1 h 80 °C
DBP: ● uncured ■ 1 h 80 °C

at 40 °C with 53% r.h. and at 40 °C with 75% r.h. The zero order release rate constants k_r^o [%/h] are plotted versus the storage time (Figs. 13–15). The release rate constants are calculated from the linear portion of the release profiles between 20 and 80% release. Exceptions are diffusion pellets with DBP and HPMC after storage at 40 °C. The range for the k_r^o calculation is then 15–40% release after storage at 53% r.h. and 20–60% after storage at 75% r.h. The standard deviations of the release rate constants are below 0.6% and are not marked.

Storage at RT causes a decrease in release rates only in the case of uncured coated pellets. These alterations are more pronounced with the pore former HPMC than with HEC (Fig. 13). In contrast to the results with 15% HEC, the release rate constants for cured and uncured products with 20% HPMC differ considerably, even after 24 months storage. As expected, intensively cured pellets show nearly constant release rates during storage, in spite of the fact that pellets with HPMC in the coating are not completely cured to the limiting release rate [21].

Storage at 40 °C and 53% r.h. has a strong influence on uncured pellets (Fig. 14). After three months a limiting value of the release rate constant is attained, independent of curing and type of pore former. This limiting value stays stable for the following months. Again, it is different for TEC and DBP with the pore former HPMC, but nearly the same with HEC.

Storage at 40 °C and 75% r.h. gives comparable changes in the release rate constants of uncured pellets as does storage at 40 °C and 53% r.h. Again, the cured pellets are stable (Fig. 15). With HPMC as pore former and, in the case of TEC as plasticizer, with HEC when cured at 80 °C, the release rate constants are somewhat higher than

after storage at 40 °C and 53% r.h. This is attributed to visible crack formation in the coating after dividing pellet aggregates which stick together. Furthermore, during storage at 75% r.h. a partial transition of theophylline to theophylline monohydrate occurs as demonstrated by DSC measurements [21]. At the same time, the volume of the theophylline pellets increases, inducing expansion of the coating and possibly crack formation, too.

These results are in general confirmed by analogous investigations with 10% HPMC and HEC [21].

A comparison of the release stability of uncured and cured diffusion pellets reveals that only sufficient curing results in stable products. The decrease in release rate and the attainment of a stable limiting value in the case of uncured diffusion pellets proceeds much faster at higher storage temperatures and humidities in comparison to RT without increased humidity (Figs. 13–15). At RT, uncured diffusion pellets exhibit a slow but distinct decrease of the release rates, although the Tg of the coating (Table 2) is above RT and the polymer is in the glassy state. However, further gradual coalescence may occur even under these conditions [1, 41–45]. According to Hancock et al. [24, 46], amorphous polymers show a certain mobility of molecule segments at temperatures up to 50 °C below the Tg.

Independent of previous curing, all diffusion pellets attain the release profile of sufficiently cured preparations after no more than three months of storage at 40 °C and 53% r.h. This result confirms the possibility of reaching the limiting release profile also by short-term application of higher relative humidity at lower temperatures [47].

3. Experimental

3.1. Coating

Eudragit® RS 30 D, Röhm GmbH, Germany, an 30% aqueous dispersion of poly(ethyl acrylate methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1 : 2 : 0.1; 150000 with 0.25% sorbic acid is used as film former. Plasticizers are triethyl citrate (TEC) and dibutyl phthalate (DBP) (Boehringer-Ingelheim and Riedel-de Haën, respectively, both Germany). Hydroxypropyl methylcellulose, Pharmacoat® 603 (HPMC) (Shin-Etsu/Syntapharm, Germany) and hydroxy ethylcellulose, Tylose® H 10 (HEC) (Hoechst, Germany) are used as pore formers.

3.2. Determination of the MFT

Equipment: Temperature gradient test device Thermostair BL-MFT"D" (Coesfeld, Germany). The temperature gradient is 20 °C. The metal plate is layered with 1.2-propanediol and covered with aluminum foil to prevent problems with cleaning. Three parallel, 20 mm wide and 300 µm thick layers of the dispersion are spread on the aluminum foil, using a doctor blade. The determination of the MFT is carried out according to DIN 53787.

3.3. Thermal analyses

3.3.1. Preparation of the films

3 to 5 ml of the dispersions are poured on a Teflon® plate. The area is limited to $10 \times 10\ cm^2$ by Tesa® strips. The layers of the dispersions are dried and cured in an oven at different temperatures above the MFT for different times. The resulting films are easily stripped from the warm Teflon® plate and stored over silica gel. The thickness of the films varies between 60 and 130 µm.

3.3.2. DSC measurements

Equipment: Mettler TA 3000 (Mettler Instruments, Greifensee, Switzerland) with TC 10 A processor and DSC measuring cell. The determinations are carried out with a heating rate of 20 °C/min, a starting temperature of −50 or −20 °C and an end point of 120 or 150 °C, using nitrogen as washing gas. About 20 mg of the film are transferred into perforated aluminum crucibles which are closed by cold-welding. The Tg is determined at 50% transformation (midpoint) after the second heating.

Table 3: Coating conditions

Filling charge	250 g pellets
Air flow	190 m^3/h
Bed temperature*	40 °C
Spraying pressure	0.6 bar
Spraying rate	1.3 g/min (1st to 5th min)
	2.3 g/min (6th to 10th min)
	3.7 g/min (main phase)
Spraying time	ca. 45 min

* 7 to 25 °C above the MFT (see Table 1)

3.3.3. TMA measurements

Equipment: Mettler TA 3000 with TC 10 A processor and TMA 40 measuring cell. The applied force for the penetration methode is 0.5 N. The heating rate is 2, 5 and 10 °C/min in the case of films without pore formers, for investigation of the influence of curing and storage on pore former containing films, and with films of HPMC and HEC alone, respectively. Washing gas is nitrogen with a rate of 200 ml/min, liquid nitrogen is used for cooling. For better comparison of the penetration curves of different films, the curves are drawn as standardized to a film thickness of 100 µm.

3.4. Diffusion pellets

3.4.1. Starting material

Starting material are theophylline pellets (Granulat SR/Pellets, Boehringer-Ingelheim), with a nucleus of saccharose, theophylline content 80.9 ± 0.16% (n = 3) [21]. They are classified into the size 1.0 to 1.4 mm.

3.4.2. Coating in the fluidized bed

Equipment: fluidized bed coating apparatus Strea I (Aeromatic, Switzerland) with stainless steel spray tower and bottom-spray gas-atomizing nozzle. A high air flow rate is obtained by complete opening of the outlet lid and is measured with an anemometer (Testovent 4300, Testoterm, Germany). The temperatures of the inlet and outlet air are measured by sensors incorporated in the Strea I, and the bed temperature by a T 432-1 thermocouple with a Therm 4201 (Ahlborn Mess- und Regeltechnik, Germany) as indicating instrument. The coating conditions are given in Table 3.

The inlet air is adjusted to 22 ± 1 °C and 40 ± 2% r.h., because marked differences in air humidity influence the batch to batch variability of the product [48, 49]. Before spraying, the pellets are warmed up for 5 min at 40 °C while mixing in the Strea I. During that time, electrostatic charging is observed which disappears after spraying.

3.5. Release

3.5.1. Release conditions

Equipment: paddle apparatus according to Ph.Eur. 1997 combined with a Lambda 2 UV/VIS spectrophotometer with continuous flow cell and automatic cell changer (Perkin Elmer, Germany) and PC. The solution is pumped through a Reagent-Filter (Braun-Lübbe, Germany) by a STA-multichannel roller pump (Desaga, Germany) with a rate of 7 ml/min, using Tygon® tubing in the pump and PTFE tubing for all other connections. As release medium 1 l of 0.1 N-HCl at 37 ± 0.5 °C is used. The theophylline released from 100 mg of coated pellets is recorded every 10 min. The stirring speed of the paddle is adjusted to 150 rpm.

3.5.2. Release from single diffusion pellets

The study is performed with the same equipment as described above. However, the paddle apparatus is replaced by a smaller thermostatic double-walled vessel with 100 ml 0.1 N-HCl and a smaller blade, stirring at 50 rpm [6].

3.6. Storage

The diffusion pellets are filled into brown glass bottles after curing and stored at RT without humidity conditioning. Additionally, 5 g of each product are stored in small petri dishes in hygrostatic boxes, deposited in a B 40 precision incubator (Memmert, Germany) at 40 °C. The relative humidities of 53 and 75% r.h. are obtained with saturated solutions of NaBr and NaCl, respectively [50].

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Prof. Dr. B.C. Lippold
Institut für Pharmazeutische Technologie
der Heinrich-Heine-Universität
Düsseldorf
Universitätsstr. 1
40225 Düsseldorf